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| 10/764,628 | 01/26/2004 | Veronique Trochon | 1002-04 | 9953 |

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| EXAMINER | |
|---|---|
| MARVICH, MARIA | |
| **ART UNIT** | **PAPER NUMBER** |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/764,628 | TROCHON ET AL. | |
| | Examiner | Art Unit | |
| | Maria B. Marvich, PhD | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *3 and 13-23* is/are pending in the application.

4a) Of the above claim(s) *3* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/12/07 has been entered.

Claims 1, 2 and 4-12 have been cancelled. Claim 3 is withdrawn. Claims 13-23 have been added and are pending in this application.

### *Claim Objections*

Claims 16, 20 and 22 are objected to because of the following informalities: claims 16, 20 and 22 recite that the "disintegrin domain is Met-420 to Glu-511 of SEQ ID NO:1. However, this numbering reflects the amino acid numbering of the full-length protein and not of SEQ ID NO:1 as Met-420 corresponds to amino acid one of SEQ ID NO:2. It would be remedial to recite Met-420 to Glu-511 of metargidin, which is SEQ ID NO:1. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112, second paragraph*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 recites the limitation "the disintegrin domain" in claim 22. There is insufficient antecedent basis for this limitation in the claim.

***Claim Rejections - 35 USC § 112, first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-23 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of direct administration of the disintegrin domain, which is Met 420 to Gly 511 of metargidin which corresponds to SEQ ID NO: 1 at a site to be targeted for diminution of the number of intratumoral vessels, for inhibition of growth of melanoma and for inhibition of pulmonary metastases, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record in the office action mailed 7/28/06 and 1/25/07 and restated below. The rejection has been slightly reworded based upon applicants' amendment.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The instant claims are drawn to a methods of inhibiting angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis by administration of a nucleic acid comprising a polynucleotide sequence of SEQ ID NO:1. The nucleic acid is inserted into an expression vector and is "present in cells transformed by said molecule in a manner to express all or part of a disintegrin domain". Hence the claims are broad in that there is a number of disease and conditions to be treated of broad scope wherein the method comprises a single step of "administering a therapeutically effective amount of an active" of the nucleic acid comprising **a** polynucleotide sequence of SEQ ID NO: 1. A polynucleotide sequence of SEQ ID NO:1 can be any so long as it is dinucleotide of SEQ ID NO:1. It is highly unpredictable that any dinucleotide can mediate the recited functions. Claims 15 and 19 recite that the nucleic molecule is present in transformed cells in a manner to express all or part of a disintegrin domain. However, without specifying a sequence of SEQ ID NO:1 comprises the disintegrin domain it is unpredictable that a part of the disintegrin domain will be expressed. If the whole of SEQ ID

NO:1 is introduced into the cell it is unclear how only part of the disintegrin domain will be expressed selectively.

The adamalysin family functions in proteolysis, adhesion, fusion and intracellular signaling (see Ruben et al, US 2002/0182702 ¶ 1042). The art teaches that there are two subfamilies of adamalysins 1) snake venom metalloproteases (SVMPs) and 2) the ADAMS (proteins with a disintegrin domain and a metalloprotease domain). Multiple ADAMS have been identified including ADAM1, ADAMTS-1, fertilin (ADAM2), cryitestin (ADAM3), epididymal apical protein I, meltrin, MS2, TNF-a converting enzyme, Kusbanian and metargidin (see Ruben et al, ¶ 0004). Within the ADAMS, the disintegrin domain functions to prevent integrin-mediated cell to cell and cell to matrix interactions such as plated aggregration, adhesion, migration of tumor cells or neutrophils or angiogenesis. There have been multiple propositions that members of the adamalysin family have a potential to treat a myriad of conditions such as those recited here (see Ruben et al US 2002/0165377 and Young et al (US 2003/0194797 in which the role of ADAM-22 and any other ADAM protein in inhibiting angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis is proposed), but these propositions have not lead to the identification of any treatments that are viable options against diseases. The specification states that metargidin comprises AMEP (anti-angiogenic metargidin peptide) and is a human protein with multipotent function including blocking angiogenic functions of integrin alpha v beta, inhibition of migration and formation of capillary structures and functions proapototically independent of modification of their cell cycle. The disintegrin domain constitutes Met 420 to Gly 511 of SEQ ID NO:1. Applicants synthesize AMEP in

bacteria and demonstrate that this protein can function to inhibit adhesion of fibrinogen to vitronectin and fibronectin, inhibit endothelial cell migration, proliferation, capillary formation and stimulates proapoptosis in endothelial cells *in vitro*. *In vivo,* AMEP nucleic acid was electrotransferred to muscle of nude and C57B1/6 mice and inhibited growth of MDA-MB-231 tumor growth and formation of pulmonary metastases in syngeneic mice.

The enablement of the instant invention has been assessed in light of the specification and the prior art available at the time of filing. "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). In the instant case, there are multiple inoperative embodiments when considering the use of the instant invention in humans such as

The instant invention is unpredictable for inhibiting angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis in humans for the following reasons. First, applicants' invention is based upon the premise that the disintegrin domain of amadalysin can be used therapeutically to treat a variety of conditions. The claims are directed to a broad and diverse genus of "administering a therapeutically effective amount of an active" of the nucleic acid comprising **a** polynucleotide sequence of SEQ ID NO: 1. A polynucleotide sequence of SEQ ID NO:1 can be any so long as it is dinucleotide of SEQ ID NO:1.

The specification is directed specifically to the analysis of AMEP, the disintegrin domain of metargidin encoded by Met 420 to Gly 511 of metargidin SEQ ID NO:1. As well, the invention is practiced using this peptide and the results do not demonstrate any understanding of the mode of action or the general nature of the effects of AMEP, (¶ 0093) "The set of results obtained show that AMEP possesses an antiangiogenic activity that is greater than that of the 1.4-kDa peptide. Given that both AMEP and the 1.4-kDa peptide possess an RGD sequence implicated in bonding endothelial cells to alpha v beta 3 integrins, we believe that the action of AMEP is not limited to blocking the functions of the alpha v beta 3 integrin. AMEP appears to possess its own activity which could be linked to modifications of the signalization at the cellular level (message that could be transported by the integrin alpha v beta 3 and/or metargidin).". The disclosure does not provide adequate guidance for the use of any part of SEQ ID NO:1 and hence the recited goals are highly unpredictable. Therefore, the efficacy of the instant invention lies in the use Met 420 to Gly 511 of metagardin which is SEQ ID NO:1 and while the structural requirements for this peptide alone have been demonstrated, the specification has not demonstrated what sequences can be used to mediate the same activity. Applicants do not demonstrate nor is it known in the art that this peptide can mediate all of the recited functions as applicants have only demonstrated that the number of intratumoral vessels can be reduced. Applicants recite that these sequences can treat cancer, inflammatory disease, atherosclerosis, macular degeneration and psoriasis. Of these, applicants have demonstrated that tumor growth alone can be inhibited. As well, the mechanism of action (or actual functional requirements) are unknown which exacerbates the ability to identify those sub regions required to mediate the function that leads to the effects noted in the application.

Secondly, the method of delivery of polynucleotides is highly unpredictable to date. Gene delivery has been a persistent problem for gene therapy protocols and the route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. Verma et al speak to the problem that is confronted in the art when they teach (Verma and Somia, Nature, September 1997), "The Achilles heel of gene therapy is gene delivery... the problem has been an inability to deliver genes efficiently and to obtain sustained expression". To present date, no generic mode of gene transfer has provided a viable option for successful gene therapy protocols, which exacerbates the broad and diverse treatments proposed by applicants. In view of predictability of the art to which the invention pertains and the lack of established protocols and the inability to predict successful administration of the broad genus of molecules: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

***Response to Argument***

Applicants traverse the claim rejections under 35 U.S.C.112, first paragraph on page 11 of the amendment filed 6/18/07 and in the Declaration filed 6/18/07. Applicants' arguments filed 6/18/07 have been fully considered but they are not persuasive for the following reasons.

The Declaration under 37 CFR 1.132 filed 6/18/07 is insufficient to overcome the rejection of claims 1, 2 and 4-12 based upon 112 first paragraph as set forth in the last Office action because: the Declaration teaches use of a plasmid coding for the AMEP gene however, the claims are directed to use of a polynucleotide sequence of SEQ ID NO:1. Secondly, applicants demonstrate in a mouse metastatic model that tumor growth was inhibited and in a melanoma model that tumor growth again was inhibited. It cannot be reasonably concluded that the mice models functions as a correlative model for treatment of psoriasis or inhibition of metastasis or invasion or treatment of all cancers. The Declaration demonstrates that intratumoral injection leads to reduced tumor growth, which may lead to a decrease in incidence of metastasis. Metastasis is outgrowth of a tumor to other sites, simply by reducing tumor growth, metastasis is not inhibited. Rather, applicants have demonstrated that intratumoral injection leads to reduced tumor growth, which may lead to a decrease in incidence of metastasis. But this is distinguishable from the event of inhibiting directly metastasis. Similarly, decreasing tumor growth however may decrease the incidence of tumor invasion, tumor invasion is not directly inhibited. Ultimately, the methods utilized *in vivo* required direct administration of SEQ ID NO:1 intratumorally to reduce tumor growth.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for

patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 13-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Ruben et al (US 2002/0165377; see entire document). **This rejection is maintained for reasons of record in the office action mailed 7/28/06 and 1/25/07 and restated below.**

Rubens et al teach treatment of medical conditions using Adam polynucleotides (¶ 0420) such as angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis (see ¶ 0084-0083). According to ¶ 0004, a ADAM protein includes metargidin. While SEQ ID NO:1 is not disclosed, the ADAM molecules are related such that a derivative of SEQ ID NO;1 is encompassed by the molecules disclosed in Rubens et al. Cells are transformed with vectors comprising the genes to express the disintegrin domain (see e.g. ¶ 0179-0183).

Claims 1, 2 and 4-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Fanslow et al (US 2006/0177443; see entire document). **This rejection is maintained for reasons of record in the office action mailed 1/25/07 and restated below.**

Fanslow et al teach treatment of medical conditions using Adam –15 or metargidin polynucleotides (¶ 0041) such as angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis (see ¶ 0065-0070). While SEQ ID NO:1 is not disclosed, the ADAM-15 include RGD and are related such that a derivative of SEQ ID NO;1 is encompassed by the molecules disclosed in Fanslow et al (¶ 0007).

***Response to Argument***

Applicants traverse the claim rejections under 35 U.S.C. 102 on pages of the amendment filed 6/18/07. Applicants' arguments filed 6/18/07 have been fully considered but they are not persuasive for the following reasons. The claims recite that the nucleic acid comprises a polynucleotide sequence of SEQ ID NO:1. Any of a number of dinucleotides appearing in the inventions of Fanslow et al and Rubens et al will be found in SEQ ID NO:1.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1633